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| EXAMINER | |
|---|---|
| EMCH, GREGORY S | |

| ART UNIT | PAPER NUMBER |
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| 1649 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/643,589 | PITTMAN ET AL. | |
| | Examiner | Art Unit | |
| | GREGORY S. EMCH | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 May 2010 and 20 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,8,12-58,85-87,93 and 94* is/are pending in the application.

4a) Of the above claim(s) *32-41,45-58 and 85-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,12-31,42-44,93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 19 May 2010 has been entered.

### *Response to Amendment*

Claim 1 has been amended, and new claims 93 and 94 have been added as requested in the amendment filed on 19 May 2010. Following the amendment, claims 1, 8, 12-58, 85-87, 93 and 94 are pending in the instant application.

Claims 32-41, 45-58 and 85-87 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the replies filed on 24 August 2006 and 23 July 2007.

Claims 1, 8, 12-31, 42-44, 93 and 94 are under examination in the instant office action.

### *Withdrawn Rejections*

The rejection of claims 1, 8 and 19 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,864,018 to Morser et al., and as evidenced by Neeper et al. (J Biol Chem. 1992) and Mjalli et al. (US 2006/0078562 A1) is withdrawn in response to the amendment of said claims to recite that the immunoglobulin element comprises at least one sequence selected from: an immunoglobulin heavy chain, an Fc domain, and a CH1 domain, wherein said fusion protein binds to a RAGE ligand.

Remaining issues are set forth below.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicants are advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 8, 13 and 19 stand rejected and claim 93 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,864,018 to Morser et al. (issued 26 January 1999; filed 16 April 1996; citation AA on IDS dated 01 March 2004), in view of Neeper et al. (J Biol Chem. 1992; Citation U on PTO-892 dated 18 March 2009), and further in view of Peppel et al. (J Exp Med 1991; citation U on PTO-892 dated 18 October 2007).

Morser teaches RAGE polypeptides including RAGE, fragments and derivatives of full length RAGE, e.g. soluble RAGE (sRAGE) and fusion proteins comprising any of these RAGE polypeptides (see col.5, lines 3-32; col.8, lines 7-29). Examples of RAGE polypeptides include Morser's SEQ ID NO: 2 (residues 1-340 of RAGE) and Morser's SEQ ID NO: 4 (residues 23-340 of RAGE, see columns 29-34). The instant specification teaches that a peptide comprising residues 1-329 of RAGE also comprises Ig1, Ig2 and Ig3 domains (see Figure 5). Thus, Morser's SEQ ID NO: 2 meets this

limitation in claim 8. Morser teaches pharmaceutical compositions comprising the RAGE polypeptides and a pharmaceutically acceptable carrier (see col.19, lines 21-24 and col.20, lines 12-20), as in claim 19. The difference between the disclosure of the Morser and the claimed invention is that the patent does not teach a fusion protein comprising a RAGE-LBE consisting of residue 1-344 of SEQ ID NO: 7 and an immunoglobulin heavy chain, an Fc domain, or a CH1 domain.

However, Neeper teaches that the extracellular (i.e. soluble) domain of human RAGE is amino acids 1-344 of RAGE (see Figure 4, p.15002). Neeper teaches that there are likely several types of AGE-biding proteins (of which soluble RAGE polypeptides are examples) potentially recognizing different AGE ligands or activating distinct cellular processes following formation of the ligand/receptor complex (see p.15003, 3rd full paragraph). Neeper does not teach a fusion protein comprising residues 1-344 of SEQ ID NO: 7 and an immunoglobulin heavy chain, an Fc domain, or a CH1 domain fused to the RAGE-LBE.

However, Peppel teaches fusion proteins comprising a soluble extracellular receptor moiety of TNF-α linked to an immunoglobulin element, wherein the immunoglobulin element comprises the $C_H2$ and $C_H3$ domain of human IgG1, i.e. the Fc domain (p.1483, paragraph 3 – p.1484, paragraph 4), as in claims 1 and 13. Peppel teaches that the fusion protein is an effective inhibitor of the ligand-receptor interaction (entire document, e.g. abstract). Furthermore, Peppel teaches that truncated receptor molecules, i.e. fragments that lack the transmembrane or cytoplasmic domains, are capable of interacting with TNF and can act as antagonists of TNF and as reagents to

be used in defining the interaction between TNF and its receptor (ligand/receptor). Peppel teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). Peppel does not teach a fusion protein comprising residues 1-344 of SEQ ID NO: 7.

As evidenced by Morser, the artisan of ordinary skill would have known that the interaction between AGE and RAGE is implicated in numerous pathological disease states and that improved inhibitors of this interaction, e.g. soluble RAGE polypeptides would be desirable (see col.5, lines 3-32; col.8, lines 7-29). As evidenced by Neeper, the artisan of ordinary skill would have known that soluble RAGE is residues 1-344 of SEQ ID NO: 7 and that AGE ligands bind to multiple proteins (see Figure 4, p.15002; p.15003, 3rd full paragraph). As evidenced by Peppel, the artisan of ordinary skill would have recognized the desirability creating a construct, which comprises a soluble extracellular receptor moiety linked to an Fc domain of an immunoglobulin for inhibiting a ligand-receptor interaction (p.1483, paragraph 3 – p.1484, paragraph 4).

Given that Morser teaches that RAGE-LBE fusion proteins, including soluble RAGE fusion proteins, are useful inhibitors of AGE/RAGE interaction, given that Neeper teaches that soluble RAGE is residues 1-344 of human RAGE and given that Peppel teaches that an extracellular receptor moiety-Fc fusion protein is an effective inhibitor for the ligand-receptor interaction, it would have been reasonable to predict that a fully functional fusion protein comprising the RAGE polypeptide disclosed by Morser and

Neeper and comprising the Fc fragment taught by Peppel et al. could be successfully produced and used for treatment of inflammatory disease. This is because Morser's disclosure concerning RAGE is analogous to Peppel's disclosure concerning TNF. See for example, col.1, lines 40-64 of Morser, which teaches that the AGE/RAGE interaction is implicated in the inflammatory response, where it leads to activation of TNF inflammatory cascades. Morser teaches that a soluble RAGE polypeptide is useful as an inhibitor of the ligand/receptor interaction (i.e. AGE/RAGE interaction) which is implicated in inflammatory disease. Similarly, Peppel teaches that a soluble TNF receptor is useful as an inhibitor of the ligand/receptor interaction (i.e. TNF/TNF receptor interaction) that is implicated in the same inflammatory pathway as RAGE in inflammatory disease. Therefore, both references teach using extracellular potions of the receptors as blocking agents of the ligand/receptor interaction for the same inflammatory pathway. Accordingly, one of ordinary skill in the art would have found it obvious to attempt to generate a RAGE fusion protein linked to an IgG immunoglobulin domain because Peppel teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). Moreover, Morser's explicit example of a soluble RAGE polypeptide (i.e. comprising 1-340 of SEQ ID NO: 7) only differs by 4 amino acids from that of Neeper. The artisan of ordinary skill would have been motivated to substitute residues 1-344 of RAGE in place of residues 1-340 because Morser discloses using the soluble portion of RAGE in general (col.5, lines 3-32; col.8, lines 7-29) and Neeper

demonstrated that residues 1-344 make up the soluble portion of RAGE (Figure 4). Such a molecule would meet the functional limitations of claim 93, i.e. the molecule would bind to either S100 or amphoterin, since it would meet the structural requirements of the claimed fusion protein. Thus, it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to improve Morser's soluble RAGE fusion protein as disclosed by Neeper and Peppel to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp (see KSR International Co. v. Teleflex Inc. (KSR), 550 U.S. ____, 82 USPQ2d 1385 (2007).

In the reply filed on 19 May 2010, applicants assert that Morser and Neeper fail to teach an immunoglobulin element selected from an immunoglobulin heavy chain, an Fc domain and a CH1 domain and fails to teach a RAGE-LBE which consists of amino acid residues 1 through 344 of SEQ ID NO: 7, as recited in claim 1. Applicants assert that Neeper fails to teach a fragment of RAGE such as the RAGE-LBE which consists of residues 1-344 of SEQ ID NO: 7. Applicants assert that Peppel describes a chimeric protein comprising a TNF receptor and an Fc domain and are entirely silent on the RAGE protein. Applicants assert that the combination of references fails to provide any motivation or reasonable expectation of success for an artisan of ordinary skill to modify Morser's RAGE polypeptides to arrive at the claimed RAGE-LBE fusion proteins. Applicants assert that none of the references provide a teaching or suggestion to modify RAGE polypeptides to improve their suitability or efficacy for any application. Applicants

assert that there is no common connection between the cited disclosures that would have motivated an artisan of ordinary skill to combine these teachings to make RAGE-LBE fusion proteins such as those claimed in the present application. Applicants assert that none of the cited references provide any guidance on how to modify the RAGE protein to arrive at the claimed invention.

Applicants' arguments have been fully considered and are not found persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Neeper teaches the claimed RAGE-LBE of residues 1-344 of SEQ ID NO: 7 and that there are likely several types of AGE-biding proteins (of which soluble RAGE polypeptides are examples) potentially recognizing different AGE ligands or activating distinct cellular processes following formation of the ligand/receptor complex (see p.15003, 3rd full paragraph). Given these teachings, the artisan of ordinary skill would have at least been motivated to try to use a polypeptide consisting of residues 1-344 of SEQ ID NO: 7 to optimize the general disclosure of RAGE fusion proteins disclosed by Morser. Morser's explicit example of a soluble RAGE polypeptide (i.e. comprising 1-340 of SEQ ID NO: 7) only differs by 4 amino acids from that of Neeper. The artisan of ordinary skill would have been motivated to substitute residues 1-344 of RAGE in place of residues 1-340 because Morser discloses using the soluble portion of RAGE in general (col.5, lines 3-32; col.8, lines 7-29) and Neeper demonstrated that residues 1-

344 make up the soluble portion of RAGE (Figure 4).

Regarding applicants' assertion that Morser provides no teaching or suggestion that RAGE polypeptides need to be further modified, the fusion proteins are taught as potentially useful in providing for enhanced expression of the RAGE polypeptide constructs, or in producing RAGE polypeptides having other desirable properties, e.g., labeling groups, e.g., enzymatic reporter groups, binding groups, antibody epitopes, etc. This general disclosure of potential uses for the fusion proteins of Morser would motivate the artisan to search the art for more specific polypeptides for inclusion with said fusion proteins. Additionally, applicants' assertion that there is no common connection between the cited disclosures that would have motivated the artisan of ordinary skill to combine these teachings is inaccurate. As set forth above, Morser teaches that the AGE/RAGE interaction is implicated in the inflammatory response, where it leads to activation of TNF inflammatory cascades (col.1, lines 40-64). This suggests that blocking either TNF signaling or AGE/RAGE signaling would be useful to treat inflammation. Moreover, Morser teaches that a soluble RAGE polypeptide is useful as an inhibitor of the ligand/receptor interaction (i.e. AGE/RAGE interaction) that is implicated in inflammatory disease. Similarly, Peppel teaches that a soluble TNF receptor is useful as an inhibitor of the ligand/receptor interaction (i.e. TNF/TNF receptor interaction) that is implicated in inflammatory disease. Therefore, both references teach using soluble, extracellular potions of the receptors as potential blocking agents of the ligand/receptor interaction that is implicated in the same inflammatory cascades in inflammatory disease.

Accordingly, one of ordinary skill in the art would have found it obvious to attempt to generate a RAGE fusion protein linked to an IgG immunoglobulin domain because of the advantages of doing so as taught by Peppel. Peppel teaches the desirability (e.g. increased stability and ease of purification) of engineering a chimeric protein in which the extracellular domain of the receptor, which normally engages the ligand, is covalently linked to IgG immunoglobulin domains (p.1483). At the time of the invention, all of the reagents were readily available and the technology existed to prepare fusion proteins as claimed and Peppel had demonstrated success in producing fusion proteins useful for therapeutic purposes with no loss of function. It would have been customary for an artisan of ordinary skill to determine the optimal fusion protein partner for inclusion with the RAGE-LBE given Peppel's explicit teachings of how to design such. Thus, one skilled in the art could have readily modified the RAGE-LBE containing fusion proteins of Morser by optimizing them for therapeutic use as taught by Neeper and Peppel. Moreover, the motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose (MPEP §2144.07). Based on the analogous disclosures of the prior art references of record, it would at least be obvious to try generate the claimed fusion protein, which is proper to support a finding of obviousness under 35 U.S.C. 103(a). See the Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

Claims 1, 8, 12-31, 42-44, 93 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,864,018 to Morser et al., in view of Neeper et al. and Peppel et al. as applied to claims 1, 8, 13 and 19 above, and further in view of U.S. 20020102604 to Milne Edwards et al. (citation A on PTO-892 dated 26 September 2006; published 01 August 2002, filed 07 December 2000) and as evidenced by WO 94/10308 to Spriggs et al. (citation N on PTO-892 dated 26 September 2006; published 11 May 1994).

The limitations of claims 1, 8, 13, 19 and 93 are addressed above. Morser Neeper et al. and Peppel et al. references teach as set forth above. The references fail to teach the remaining elements of claims 12, 14-18, 20-31 and 42-44.

However, Milne Edwards (U.S. 20020102604) teaches fusion proteins comprising polypeptides of the invention and functional fragments thereof for the treatment of inflammatory disorders (e.g. paragraphs 0117, 0176, 0230 and 0708). The reference teaches antibodies and fragments thereof, (including heavy chains [VH], Fc domains and CH1 domains) as potential partners in the fusion proteins (paragraphs 0364, 0376 and 0377), as in claims 12 and 14-16. Milne Edwards teaches that the fusions can comprise any combination of the above-mentioned antibody fragments or domains (0376 and 0377), as in claim 16. Milne Edwards teaches dimerizing polypeptides, including leucine zippers, as part of the fusions proteins of the invention and teaches that these dimerizing polypeptides are useful to create soluble multimeric fusion proteins, which may offer the advantage of enhanced biological activity (0312-

0315), as in claims 18, 20, 27, 31 and 94. Also, at paragraph 0314, Milne Edwards states "examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference." Accordingly, Spriggs (WO 94/10308) teaches jun and fos leucine zippers (p.1, line 34 – p.2, line 2), as in claims 28 and 29. Milne Edwards teaches stabilizing polypeptides (1260), targeting polypeptides (1679), and purification polypeptides (0176) as part of the fusion proteins of the invention, as in claim 20. Milne Edwards also teaches that the dimerizing polypeptide can be amphiphilic polypeptides and fragments thereof as part of the fusion proteins (1679), as in claim 21, and teaches that fragments of polypeptides can be at least 6, at least 8 to 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 350, 400, 450 or 500 amino acids (0333), as in claims 22-25. Milne Edwards teaches a peptide helix bundle (0671), as in claim 26, and teaches that formation of multimers (e.g. dimerization) can be the result of ionic interaction (i.e., oppositely charged polypeptides bound to each other; 0312), as in claim 30. Milne Edwards teaches protein complexes, comprising a protein of the invention (e.g. 0667), as in claim 42. Milne Edwards teaches TNF-α inhibitors (e.g., uromodulin) as part of pharmaceutical compositions of the invention (para. 0825), as in claims 43 and 44.

None of the cited references teach a fusion protein, wherein said immunoglobulin element comprises a CH1 domain of a first immunoglobulin class and a CH1 domain of a second immunoglobulin class, wherein the first and second immunoglobulin classes are not the same. However, in the instant case this is clearly a result effective

parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ (see MPEP § 2144.05). It would have been customary for an artisan of ordinary skill to determine the optimal immunoglobulin composition of the fusion protein of claim 17 by varying the immunoglobulin type in order to best achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, this optimization of immunoglobulin type would have been obvious at the time of applicants' invention.

As evidenced by Morser, the artisan of ordinary skill would have known that the interaction between AGE and RAGE is implicated in numerous pathological disease states and that improved inhibitors of this interaction would be desirable. As evidenced by Neeper, the artisan of ordinary skill would have known that soluble RAGE is residues 1-344 of SEQ ID NO: 7 and that AGE ligands bind to multiple proteins (see Figure 4, p.15002; p.15003, 3rd full paragraph). As evidenced by Peppel, the artisan of ordinary skill would have recognized the desirability creating a construct, comprising a soluble extracellular receptor moiety linked to an Fc domain of an immunoglobulin for inhibiting a ligand-receptor interaction. As evidenced by Milne Edwards and Spriggs, the artisan of ordinary skill would have been motivated to include the fusion protein partners disclosed therein with RAGE-LBEs because Milne Edwards teaches that these would provide soluble multimeric fusion proteins with increased biological activity for treatment of inflammation (e.g. 0117, 0176, 0230, 0312-0315 and 0708). Given that Morser teaches that RAGE-LBE fusion proteins are useful as inhibitors of AGE/RAGE

interaction, given that Neeper teach that soluble RAGE is residues 1-344 of human RAGE, given that Peppel teach that an extracellular receptor moiety-Fc fusion protein is a desirable inhibitor for the ligand-receptor interaction, given that Milne Edwards teaches that the claimed fusion proteins partners are desirable and given that all of the references concern treatment of inflammatory disorders, it would have been reasonable to predict that a fully functional fusion protein comprising the RAGE polypeptide disclosed Morser and comprising the Fc fragment taught by Peppe and comprising the other partners as taught by Milne Edwards could be successfully produced and used for treatment of inflammation.

Moreover, regarding the potential fusion proteins partners of the claims (other than the RAGE-LBE polypeptides), inclusion of said partners is clearly the result of routine optimization of parameters (MPEP § 2144.05). It would have been customary for an artisan of ordinary skill to determine the optimal fusion protein partner for inclusion with RAGE-LBE given both Peppel's and Milne Edwards' explicit teachings of how to design such. At the time of the invention, all of the reagents were readily available and the technology existed to prepare fusion proteins as claimed and Milne Edwards had demonstrated success in producing fusion proteins with no loss of function and being useful for therapeutic purposes. Thus one skilled in the art could have readily modified the RAGE-LBE containing fusion proteins of Morser by optimizing them for therapeutic use as taught by Peppel and Milne Edwards. Absent some demonstration of unexpected results from the claimed parameters, this optimization of proteins would have been obvious at the time of applicants' invention. Therefore, it

would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to improve Morser's soluble RAGE fusion protein as disclosed by Peppel and Milne Edwards to yield predictable results. This is because the artisan has good reason to pursue the known options within his or her technical grasp. Such would amount to a substitution of known equivalent elements, one fusion proteins for another, to obtain predictable results.

In the reply filed on 19 May 2010, applicants assert that Morser et al. do not teach or suggest a dimerizing polypeptide, a purification polypeptide, a stabilizing polypeptide, or a targeting polypeptide as recited in claim 20. Applicants assert that Milne-Edwards et al. and Spriggs et al. are both entirely silent on the RAGE protein and that none of the references provide any teaching or suggestion to modify the RAGE polypeptides to improve their suitability or efficacy for any application and that there is no common connection between the cited references to arrive at the claimed invention.

Applicants' arguments have been fully considered and are not found persuasive. Again, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As set forth above, regarding the potential fusion proteins partners of the claims (other than the RAGE-LBE polypeptides), inclusion of said partners is clearly the result of routine optimization of parameters (MPEP § 2144.05). It would have been customary

for an artisan of ordinary skill to determine the optimal fusion protein partner for inclusion with RAGE-LBE given both Peppel's and Milne Edwards' explicit teachings of how to design such. At the time of the invention, all of the reagents were readily available and the technology existed to prepare fusion proteins as claimed and Milne Edwards et al. had demonstrated success in producing fusion proteins with no loss of function and being useful for therapeutic purposes. Thus, one skilled in the art could have readily modified the RAGE-LBE containing fusion proteins of Morser by optimizing them for therapeutic use as taught by Peppel and Milne Edwards. Absent some demonstration of unexpected results from the claimed parameters, this optimization of proteins would have been obvious at the time of applicants' invention. Such would amount to a substitution of known equivalent elements, one fusion protein for another, to obtain predictable results. Combining the teachings of the prior art of record would result in a fusion protein comprising the RAGE-LBE, and there is no reason to believe that such a fusion protein would not bind to RAGE ligands and would not be useful for therapeutic purposes.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ali Salimi, can be reached at (571) 272-0909. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.
/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
31 March 2011

/DANIEL E. KOLKER/
Primary Examiner, Art Unit 1649
April 4, 2011